UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/727,195	12/03/2003	Carmen V. Pepicelli	HUIP-P02-032	6922

28120 7590 11/09/2007

ROPES & GRAY LLP
PATENT DOCKETING 39/41
ONE INTERNATIONAL PLACE
BOSTON, MA 02110-2624

EXAMINER	
HOWARD, ZACHARY C	

ART UNIT	PAPER NUMBER
1646	

MAIL DATE	DELIVERY MODE
11/09/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/727,195	PEPICELLI ET AL.	
	Examiner	Art Unit	
	Zachary C. Howard	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 August 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-17 and 19-27* is/are pending in the application.

4a) Of the above claim(s) *5-17* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4 and 19-27* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-17 and 19-27* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *16 May 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Application, Amendments and/or Claims

The amendment of 8/27/07 has been entered in full. Claims 1-4 and 19-22 are amended. New claim 27 is added. In the 8/27/07 response, Applicants state, "[f]ollowing this Amendment, claims 1-17 and 18-27 will be pending" (pg 7). However, claim 18 was canceled previously and is indicated as canceled in the 8/27/07 claim listing (see pg 4).

Claims 5-17 remain withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected species, there being no allowable generic or linking claim.

Claims 1-4 and 19-26 are under consideration in the instant application.

Withdrawn Objections and/or Rejections

The following page numbers refer to the previous Office Action (5/16/07).

The objection to claim 21 at pg 3 for failing to further limit claim 1 is *withdrawn* in view of Applicants' amendment to the claim 21 that remove dependence from claim 1.

The rejection of claims 1-4 and 21-26 under 35 U.S.C. § 112, first paragraph at pg 10-12 for failing to comply with the written description requirement is *withdrawn* in view of Applicants' amendments to the claims.

The rejection of claims 1-4 and 22-26 under 35 U.S.C § 112, second paragraph, at pg 12-13 is *withdrawn* in view of Applicants' amendments to the claims.

The rejection of claim 21 under 35 U.S.C. §103(a) as being unpatentable over Marigo et al (U.S. Patent 6,261,786) in view of Fujita et al (1997) is *withdrawn* in view of Applicants' amendments to the claim that remove dependence from claim 1.

Maintained Objections and/or Rejections

Claim Rejections - 35 USC § 112, 1st paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 2 and 19-24 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for

(1) a method of screening for an agent for inducing the formation of, or the maintenance or functional performance of normal lung tissue, comprising contacting embryonic lung tissue from a *Shh* mutant mouse with an agent and determining, as compared to a control, whether the agent promotes hedgehog signaling and whether the agent induces the formation of, or the maintenance or functional performance of normal lung tissue, does not reasonably provide enablement for

(2) a method of screening for an agent for inducing the formation of, or the maintenance or functional performance of normal lung tissue, comprising contacting lung tissue with an amount of an agent and determining, as compared to a control, whether the agent promotes hedgehog signaling and whether the agent induces the formation of, or the maintenance or functional performance of normal lung tissue. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. This rejection was set forth at pg 3-10 of the 5/16/07 Office Action.

Applicants' arguments (8/27/07; pg 8-9) as they pertain to the rejection have been fully considered but are not deemed to be persuasive for the following reasons.

In the response, Applicants argue that in the enablement analysis "appropriate weight" has not been given to a particular determination step recited in the claim; specifically, determining "whether the agent induces the formation of, or the maintenance or functional performance of normal lung tissue" (pg 8). Applicants argue that it is immaterial whether or not the skilled artisan could predict the behaviour of the

screened agent, because the claimed method would only identify those compounds that both promote signal transduction and induce formation of maintenance or functional performance of normal lung tissue. Applicants argue that there are no inoperative embodiments encompassed by the claims.

Applicants' arguments have been fully considered but are not found persuasive. In the enablement analysis set forth previously, the determination step quoted by Applicants (see above) was fully considered and given appropriate weight. The step of "determining, as compared to a control ... whether the agent induces the formation of, or the maintenance or functional performance of normal lung tissue" does not limit the claimed method to embodiments performed solely with functional agents. First, the use of the term "whether" in the method step indicates that said "determination" encompasses two alternative results; specifically the determination that the agent either (1) *does* or (2) *does not* induce "the formation of, or the maintenance or functional performance of normal lung tissue". Thus, the method of screening encompasses distinguishing between functional and non-functional agents. Second, the claims are not limited to screening using the single type of lung tissue that was demonstrated to allow for "the formation of, or the maintenance or functional performance of normal lung tissue" when contacted by a single agent (e.g., hedgehog protein or an agent mimicking its action). As set forth previously, this single type of lung tissue is embryonic lung tissue from a *Shh* mutant mouse, which can be used in *in vivo* or *in vitro* methods wherein said tissue is contacted with a test agent and it is determined whether hedgehog/patched signal transduction was promoted (by assessing Ptc-1 or Gli-1 gene expression) and whether "normal" or functional lung tissue was formed. Instead, as set forth previously, the claims encompass a method of screening using a broad genus of types of "lung tissue"; these embodiments lack enablement for the reasons set forth in the previous Office Action (pg 5-9). In practicing the claimed method with these embodiments, it is not predictable whether or not any agent can be found that will produce the results required for the claims, and undue experimentation would be required to determine how to successfully use these other types of "lung tissue" in the claimed screening methods.

Applicants further argue that with respect to testing on cancer cells and other transgenic animals, Applicants note that "there are no inoperative embodiments in the claimed method" because the claims all require that "the agent induces the formation of, or maintenance or functional performance of normal lung tissue". Applicants argue that a "negative result" cannot be equated with an inoperative embodiment.

Applicants' arguments have been fully considered but are not found persuasive. In the previous Office Action, the term "inoperative embodiment" was not used and thus a "negative result" gathered from practicing the claimed invention was not held to be an "inoperative embodiment". As set forth previously, and reiterated herein, the claimed screening methods encompass use of genus of different types of "lung cells" which are not commensurate in scope with the single type of "lung cells" enabled for use in the claimed method by the instant specification. These embodiments may eventually be usable in the claimed screening method but would first require undue experimentation in order to use them as such.

Applicants further argue that the claims are not directed to the preparation of new transgenic animals and embryonal cells. Applicants argue that while such animals and cells could be used in the claimed methods, the claims are directed to "a general way of screening agents for the recited activities" and it is "unreasonable to require Applicants to teach how to prepare every possible organism, tissue or cell type that could be used in the claimed method". Applicants submit that, "Applicants are aware of no legal basis for such a requirement, because nearly any screening method would be rejected on a basis that has little to do with the screening method itself" (pg 9).

Applicants' arguments have been fully considered but are not found persuasive. Applicants' methods are directed to methods of use of a genus of cells including both *in vitro* and *in vivo* cells. The fact the method is intended for screening test agents for activity does not obviate the requirement for the skilled artisan to be able make and use the full scope of the genus of cells encompassed by the claims. For the reasons set forth previously, the specification does not enable the full scope of transgenic animals and embryonal cells to be used in the claimed method. Rather than having "little to do with the screening method itself", the particular type of lung cells to be used in the

screening method are integral to the success of a test agent in the claimed method in forming functional lung tissue.

Claim Rejections - 35 USC § 112, 1st paragraph, written description

Claims 19 and 20 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This rejection was set forth at pg 10-12 of the 5/16/07 Office Action.

Claim 19 depends from claim 2 and limits the "agent" to be used in the method to a "small organic molecule which binds to a patched protein". Therefore, claim 19 requires that the agent to be used in the screening method is a previously known small molecule that that binds to patched. However, the specification fails to describe any small organic molecules that bind to patched protein.

Claim 20 depends from claim 2 and limits the agent to one that mimics hedgehog. However, the only specific agents that "mimic hedgehog" described by the specification are the hedgehog proteins.

As set forth previously, adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required.

Applicants' arguments (8/27/07; pg 9) as they pertain to the rejection have been fully considered but are not deemed to be persuasive for the following reasons.

In the response, Applicants argue that the claims have been amended to "to be directed to methods for screening for "agents"" which "can be any compound contemplated by the specification". Applicants argue that no guidance on individual agents to be tested should be required for a screening method, even if dependent claims "enumerate types of agents that can be screened..." (pg 9).

Applicants' arguments have been fully considered but are not found persuasive. It is noted that the claims have been amended, and Applicants' arguments are

persuasive with respect to claims 1-4 and 22-26 (as noted above, the written description rejection for these claims has been withdrawn). However, claims 19 and 20 are directed to agents with specific structural and/or functional characteristics.

Claim 19 requires possession of an agent that is a small organic molecule that binds to patched protein in order to practice the claimed method of screening with said agent. However, the specification fails to describe any small organic molecules that bind patched. Therefore, the claim 19 fails to meet the written description provision of 35 U.S.C. §112, first paragraph.

Claim 20 requires possession of an agent that mimics hedgehog to promote hedgehog signaling in order to practice the claimed method of screening with said agent. Potential agents that mimic hedgehog include proteins, nucleic acids, carbohydrates, lipids, small organic molecules large organic molecules and other compounds. However, the specification fails to describe any particular compounds within said genus that mimic hedgehog other than the hedgehog proteins. Therefore, only hedgehog polypeptides, but not the full breadth of the claim meets the written description provision of 35 U.S.C. §112, first paragraph.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 3, 4, 25 and 26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Marigo et al (U.S. Patent No. 6,261,786, published 7/17/01, filed 7/2/96 and claiming priority to 12/30/93; cited previously) in view of Fujita et al (9/18/1997, Biochemical and Biophysical Research Communications, 238: 658-665; cited previously). This rejection was set forth at pg 13-15 of the 5/16/07 Office Action.

Applicants' arguments (8/27/07; pg 10-11) as they pertain to the rejection have been fully considered but are not deemed to be persuasive for the following reasons.

In the response, Applicants traverse the rejection and argue that the Fujita teaches only that antibodies, and not small molecules, are useful in inhibiting the growth of LK-2 lung cancer cells (pg 10). Applicants argue that in view of this, a skilled artisan would have had no reasonable expectation of success that the claimed method would be successful, and without a reasonable expectation of success the claimed method cannot be obvious in view of the cited references (pg 10-11).

Applicants' arguments have been fully considered but are not found persuasive. It is true that Fujita teaches only that antibodies, and not small molecules, are useful in inhibiting the growth of LK-2 lung cancer cells. However, the rejection under 103(a) is not based on the teachings of Fujita alone, but rather on the teachings of Marigo in view of the teachings of Fujita. As set forth previously, Marigo teaches assays (either *in vivo* or *in vitro*) for screening test compounds, including small organic molecules, to identify antagonists of hedgehog signaling that can be used to modulate "hedgehog inductive responses" in a "target cell" (the specific teachings of Marigo are set forth at pg 14 of the 5/16/07 Office Action). Marigo does not teach a method of screening using lung cancer cells. Fujita demonstrates that an antibody to the hedgehog protein blocks proliferation of said lung cancer cells, thus showing that the hedgehog signaling pathway is active in these cells and tied to proliferation of the cells (the specific teachings of Fujita are set forth at pg 14-15 of the 5/16/07 Office Action). As set forth previously, it is the combination of these teachings that render the use of the lung cancer cells taught by Fujita in the methods of screening taught by Marigo. The teachings of Marigo specifically suggest use of small organic molecules as one category of molecules to use in the methods of screening, and therefore the fact that Fujita only teaches antibodies does not detract from the reasonable expectation of success in screening for using hedgehog pathway antagonists using small organic molecules.

New rejections necessitated by Applicants' amendment

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claim 27 is rejected under 35 U.S.C. 103(a) as being unpatentable over Marigo et al (U.S. Patent No. 6,261,786, published 7/17/01, filed 7/2/96 and claiming priority to 12/30/93; cited previously) in view of Bellusci (January 1997. Development. 124: 53-63; cited as reference CB on the 12/3/03 IDS).

The recitation of "screening for an agent for inhibiting or reducing the proliferation or growth of cells" in the preamble of new claim 27 is interpreted as an intended use and bears no accorded patentable weight to distinguish the claimed method over one from the prior art. Therefore, claim 27 encompasses a method comprising contacting normal lung cells with an agent, and determining, as compared to a control, whether the agent inhibits (1) hedgehog/patched signal transduction and (2) cell proliferation. Furthermore, the term "normal lung cells" has been broadly interpreted to encompass any lung cell that is found in *in vivo* (i.e., in a "normal" location).

Marigo teaches "cell-based assays for identifying small molecule agonists/antagonists" (col 51, lines 24-25). Marigo teaches that "cells which are sensitive to hedgehog induction, e.g. patched-expressing cells, can be contacted with a hedgehog protein and a test agent of interest, with the assay scoring for anything from simple binding to the cell to modulation in hedgehog inductive responses by the target cell in the presence and absence of the test agent. As with the cell-free assays, agents which produce a statistically significant change in hedgehog activities (either inhibition or potentiation) can be identified" (col 51, lines 27-35). Marigo teaches that patched gene expression is responsive to Shh signaling. Marigo teaches that "[a]fter identifying certain test compounds as potential modulators of the target hedgehog receptor activity, the practitioner of the subject assay will continue to test the efficacy and specificity of

the selected compound both in vitro and in vivo ... for subsequent in vivo testing ... agents identified in the subject assay can be formulated in pharmaceutical preparations for in vivo administration to an animal, preferably a human".

Marigo does not teach a method of screening using "normal lung cells".

Bellusci teaches "a role for SHH in lung morphogenesis, and suggest that SHH normally regulates lung mesenchymal cell proliferation in vivo" (see Summary on pg 53). Bellusci teaches that "Shh overexpression results in an increase in epithelial and mesenchymal cell proliferation and to a lung which contains an abundance of mesenchyme and no functional alveoli" (pg 54). The specification does not use the phrase "normal lung cells"; nor does it describe a genus of "normal lung cells"; nor does it describe how to distinguish "normal" from "abnormal cells"; nor does it describe a method of using a specific genus of "normal lung cells". The phrase has been broadly interpreted to encompass any "lung cells" that are in their "normal" location; i.e., *in vivo*. Therefore, the lung cells taught by Bellusci are encompassed by the phrase "normal lung cells" because they are in their normal *in vivo* location.

It would have been obvious to the person of ordinary skill in the art at the time the invention was made to perform a method of screening comprising contacting normal lung cells taught by Bellusci with a test agent as taught by Marigo and measure hedgehog signaling (by measuring patched gene expression) as taught by Marigo and growth as taught by Bellusci. An agent that reduces hedgehog signaling and reduces the increased proliferation observed by Bellusci would be identified as an agent that inhibits the proliferation of normal lung cells. The person of ordinary skill in the art would have been motivated to do so to identify an agent that is an antagonist (inhibitor) of hedgehog signaling and lung cell growth.

Claim Rejections - 35 USC § 112, 1st paragraph, new matter

Claim 27 is also rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement because the claims contain new matter.

Claim 27 was newly entered in the 8/27/07 claim amendments filed by Applicants. Applicants' response does not appear to indicate where the specification

provides support for a description of new claim 27. Furthermore, the specification does not use the phrase "normal lung cells"; nor does it describe a genus of "normal lung cells"; nor does it describe how to distinguish "normal" from "abnormal cells"; nor does it describe a method of using a specific genus of "normal lung cells". The phrase has been broadly interpreted to encompass any "lung cells" that are in their "normal" location; i.e., *in vivo*. However, there is no support in the specification for a method that is directed to the specific genus of "normal lung cells". Therefore, the specification as originally filed lacks support for the genus of molecules encompassed by new claim 27.

Conclusion

No claims are allowed.

Applicants' amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicants are reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Zachary C. Howard whose telephone number is 571-272-2877. The examiner can normally be reached on M-F 9:30 AM - 6:00 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary B. Nickol can be reached on 571-272-0835. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

zch

/Elizabeth C. Kemmerer/
Primary Examiner, Art Unit 1646